REMARKS

Entry of the foregoing amended and new claims and favorable reconsideration of the subject application, as amended, and in light of the remarks that follow, are respectfully requested.

By the present amendment, claims 10, 13, 15, 18, 21, 22, 24, 26, 28, 31 to 35, 37, 39 to 41 and 44 have been amended. Claims 11, 16, 20, 30, 42, 43, 47 and 48 have been cancelled. Claims 50 to 55 have been added. Support for these new claims appears respectively at least on page 4 line 3, page 11 lines 3-4, page 5 line 13 and page 4 line 8, page 4 line 3 and page 6 lines 12-13 and 17, page 6 line 18, page 1 line 29-30, page 4 lines 5-8 of the specification as filed.

Claims 10, 39-41, 43-48 have been rejected under 35 U.S.C. § 112 first paragraph, as lacking written description. Claims 43, 47 and 48 have been cancelled. As far as this rejection pertains to the claims currently of record, this rejection is respectfully traversed.

In rendering this rejection, the Examiner asserts that there is no support in the specification for claim 40. Additionally, the Examiner includes a general statement that in the remaining rejected claims the Examiner has not found support in the specification and Applicants have not specifically pointed out where support could be found in the specification. In response thereto, Applicants suggest that support can be found in the specification for the rejected claims as follows:

Claim 10: The composition of the drug is disclosed at least page 4, lines 1 to 7. Regarding the route of administration of this drug, that it may be "orally" is described at least at page 6, line 17 and "subcutaneously, transdermally" at least at page 6, lines 12-13.

Claim 39 is supported by the description at least in example 2 and more specifically at least on page 11, lines 3-4.

Claim 40 is supported in the specification at least on page 5, line 13 and page 11, line 12, and in example 3. Furthermore, it is noted that claim 40 has been further amended to recite a rate of 0.2 mg of nicotine per day per kilogram of body weight.

Claim 41 is supported by the description at least on page 8.

Claim 44 is directed to administration modes of the drug which are "continuous or progressive" such as described at least on page 4, line 3.

Claim 45 is supported in the specification at least on page 7 line 20, in table 1 and page 11, lines 3-4.

Claim 46 is supported in the specification at least on page 4, lines 4-8.

It is respectfully suggested that the above claims are supported by the specification as set forth above. Thus, withdrawal of this aspect of the rejection is respectfully requested.

Claims 10-16, 18-27, 44-46 and 48 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Part of this rejection has been obviated by the cancellation of claim 11 and the amendment of claim 15. As far as the remaining claims are concerned, this rejection is respectfully traversed.

In rendering this rejection, the Examiner deems that the word "progressive" in claims 10 and 44 is not defined in the specification. However, the meaning of the term "progressive" is indicated at least page 4, lines 26-30 and page 5, lines 3-8 in the specification as filed. Furthermore, an example of "progressive" administration has been explained at page 5, lines 3 to 8. Consequently, Applicants submit that one skilled in the

art, reading the present disclosure would understand that progressive administration of the drug, as set forth in the claims, corresponds to a staged increase in dosage as disclosed in the specification at least on page 4 line, 27; *i.e.*, that the protocol of administration involves "a gradual increase in the cumulative doses of nicotine." Thus, since a person skilled in the art when reading the specification would know what the term "progressive" means, the definiteness requirement under 35 U.S.C. §112, second paragraph has been met. See, *Miles Laboratories, Inc v. Shandon Inc.*, 997 F.2d 870, 27 U.S.P.Q.2d 1123 (Fed. Cir.1993), *cert. den.* 510 U.S. 1100 (1994).

Moreover, although the Examiner deems that the word progressive is not defined in the specification, Applicants submit that an explicit definition is not required under 35 U.S.C. §112, second paragraph. As stated in the Treatise by Prof. Chisum:

> There is no requirement that each term appearing in the claim be expressly defined in the claim or specification, as long as "those skilled in the art would understand what is claimed when the claim is read in light of the specification."

(3 Donald S. Chisum, Chisum on Patents, § 8.03 [3] at footnote 4 (2002), citing *Morton Int'l, Inc. v. Cardinal Chemical Co.*, 5 F.3d 1464, 1470, 28 U.S.P.Q.2d 1195 (Fed. Cir. 1993).)

Therefore, Applicants respectfully submit that, as used in the claims, the word "progressive" can be clearly understood by a person of ordinary skill in the art, particularly when read in light of the specification. Withdrawal of this aspect of the rejection is respectfully requested.

In claim 15, it is noted that the Examiner has not found persuasive the prior arguments regarding use of the word "improving" and has instead suggest that it be replaced by the

word "restoring" which is referred to on page 3, line 11 of the specification. However, this overlooks Applicants specific description of improvements of varying scope and explicit use of the term "improvements:"

> In conclusion, comparing the results obtained with the drug of the invention, administered together with L-DOPA in sub-active doses, it appears that, for the first time, patients experience a re-establishment, reduction or complete stop to syndromes characterizing Parkinson's disease and associated diseases. The results of the UPDRS I, II and III tests also show clear re-establishment of dopaminergic and nicotinergic functions which allows long-term stabilization of these improvements to be presumed.

(Specification, p. 11, ln. 28, to p. 12, ln. 5 (emphasis added).)

In view of the above, withdrawal of these rejections is respectfully requested.

Claims 10 to 49 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Domino et al.* (hereafter "*Domino*"). As far as this rejection may pertain to the claims of record, this rejection is respectfully traversed.

To briefly review, it was known at the time of filing the present application that L-DOPA, which is converted to dopamine in the brain, was the "gold standard" for treating Parkinson's disease. In general L-DOPA has effects on Parkinson's disease, particularly it is most effective against rigidity and slowness. In return, L-DOPA produces less of a beneficial effect in the patient with regard to tremor, balance and gait. Thus, in half of patients with Parkinson's disease L-DOPA significantly improves the quality of life for many years. However, the adverse side effects of L-DOPA are considerable and well-known, including physical and psychiatric side effects.

Such adverse side effects typically occur within four or six years of treatment with L-DOPA. Furthermore, in many patients, when the drug is taken over a long period of time there is an observed decrease in efficacy and often an increase in bradykinesia (slowness) or tremor in the morning before the next due dose. Additionally, as a consequence of decreased efficacy over a period of time, it becomes necessary to increase the frequency of L-DOPA doses, which puts patients at risk for dyskinesia (the impairment of the power of voluntary movement resulting in fragmentary or incomplete movements); this condition usually occurs when the drug level peaks.

In contrast, the present invention relates to a drug composition for continuous or progressive or continuous and progressive administration to a subject orally, subcutaneously, transdermally or any combination thereof, comprising as a first component, nicotine or a nicotine derivative and comprising as a second component, L-DOPA in a dose at least 30% lower than the effective dose when L-DOPA is administered in the absence of said first component. Hence, the present invention solves the problem associated with past therapeutic methods consisting of long term and high rate dosing of L-DOPA by providing a drug composition comprising L-DOPA in a dose at least 30% lower than the effective dose when L-DOPA is administered in the absence of the first component. This at least 30% lower rate makes it possible to increase the duration of treatment by limiting bradykinesia and dyskinesia in comparison with the effective dose when L-DOPA is administered alone.

To begin with, Applicants submit that the present invention is not obvious in view of *Domino* since this publication discloses a dose of L-DOPA of 12.5 mg/kg. This dosing rate was chosen because it had previously been shown to be effective when given alone. Consequently, *Domino* merely

mimics the well-known dosing levels of L-DOPA cited in the literature. There is neither a teaching nor a suggestion in *Domino* to alter the dosage of L-DOPA and thereby limit the known side effects of this drug. To the contrary, Applicants use what would have been considered by *Domino* and others to be a sub-active dose of L-DOPA of at least 30% lower than the effective dose when L-DOPA is administered in the absence of nicotine. Thus, in the present invention, the rate of L-DOPA dosing ranges from 0.2 mg to 3 mg/kg/day. This particular range of L-DOPA, *i.e.*, at least 30% lower than the previous effective dose, not only limits the side effects, but at the same time the patients experience a reduction or complete inhibition of the syndromes of Parkinson's disease and associated diseases as demonstrated in the examples. This is a surprising result since, although one of ordinary skill in the art would expect a reduction in side effects by using a lower dosage of L-DOPA, concurrently, the skilled artisan would also expect an increase in symptoms associated with Parkinson disease in the patient. In fact, the exact opposite occurs, *i.e.*, lowering the dosage of L-DOPA decreases the symptoms associated with, for example, Parkinson disease, provided that Applicant's drug combination is used.

Furthermore, Applicants offer the following comments with respect to the prior arguments presented by the Examiner concerning the use of animal models and continuous treatment and drug combinations.

Domino describes data obtained based on Parkinson's disease induced by the use of MPTP. This animal model uses monkeys with unilateral lesioned DA neurons and is used in Parkinson's disease surveys because the animals can easily drink, feed and groom themselves using their normal hand and leg. Thus, this animal model is a humanitarian and ethical

animal model. In return, this animal model is "inadequate" according to the *Domino*'s disclosure as evidenced at least page 419, column 1, line 2. Indeed, surveys and measurements of contraversive hand movements and circling are an inadequate measure of therapeutic response. (*Domino*, p. 419, lns. 2-4.)

Furthermore, MPTP-induced Parkinson's symptoms are not equivalent to the induced idiopathic Parkinson's disease since the mechanism of appearance of the disease is unknown. The animal model in *Domino* does not induce truly molecular and cellular lesions equivalent to idiopathic Parkinson's disease lesions. Consequently, extrapolating the treatments proposed in *Domino* is uncertain at best and may not be relevant as treatment for Parkinson's disease. Thus, reliance on the *Domino* reference provides an insufficient basis on which to render the claims of the present invention obvious; furthermore, as noted, *Domino* may not be sufficient even to provide a *prima facie* basis for obviousness.

With respect to the Examiner's comments concerning continuous treatment, this means treatment without any interruption, thus permitting constant plasmatic rates of the drug composition during the day in the patient. Such continuous treatment is not necessarily obvious in the case of a chronic disease like Parkinson's disease. Indeed, prior to the filing of the present application, it was known to one of ordinary skill in the art that treatment of Parkinson's disease required reduced non-continuous doses of the L-DOPA medication. Thus, a patient had to temporarily stop taking medication to allow some recuperation of normal functions, as discussed above, and in order to maintain sufficient sensitivity to the drug. In the case of Parkinson's disease, the patient usually had to stop taking all medication for from 3-21 days and then slowly to reinitiate therapy to gradually increasing doses. Therefore, it

cannot be said that it was obvious to effect a continuous dosing treatment regimen in view of the above-described knowledge in the art.

Finally, it is observed that *Domino* tested the eventual potentiation between nicotine and dopaminergic agonists as evidenced at page 417, paragraph 2, and explained that "no synergistic or antagonistic effects with nicotine and the full dopamine D_2 receptor agonist" have been observed. Therefore, such a disclosure in *Domino* would not lead the skilled artisan to even attempt using nicotine and dopaminergic agonists as presented in the present claims of record, since no beneficial effects were observed. Rather than rendering the present invention obvious, a skilled artisan would <u>be led away</u> from the presently claimed invention by such teachings in *Domino*. The dopaminergic agonist has an effect on D_2 and D_3, D_4 and D_6 receptors and that has not been suggested by the disclosure of *Domino*. The combined features of the drug composition of the present invention mutually support unexpected and surprising results in spite of *Domino*'s poor results. Consequently, use of the combination drug composition of the present invention is clearly not obvious.

In view of the above, withdrawal of the rejection pursuant to 35 U.S.C. § 103(a) is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **<u>"Version with markings to show changes made."</u>**

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone applicant's attorney at (908) 654-5000 in

order to overcome any additional objections which she might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: January 22, 2003

Respectfully submitted,

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Version With Markings to Show Changes Made

10. (Twice Amended) A drug composition for continuous or progressive or continuous and progressive administration to a subject orally, subcutaneously, transdermally or any combination thereof, comprising as a first component, nicotine or a nicotine derivative and a second component comprising L-DOPA in a dose at least 30% lower than the effective dose when L-DOPA is administered in the absence of said first component.

13. (Twice Amended) The drug composition of claim 12 wherein said dopaminergic agonist is selected from the group consisting of bromocriptine and piribedil ~~and biperiden~~.

15. (Twice Amended) A method for improving the functionality of D1 and D2 dopaminergic receptors associated with neurodegenerative diseases, multi-systemic atrophies or both, comprising administering to a human mammal~~subject~~ over a long term period an effective dose of at least two drug components comprising a first component nicotine or a nicotine derivative, and a second component comprising ~~at least one member selected from the group consisting of~~ L-DOPA and a dopaminergic ~~agonists~~agonist.

18. (Twice Amended) The method of claim ~~[16]~~15, wherein said D1 and D2 dopaminergic receptors are associated with neurodegenerative diseases.

21. (Twice Amended) The method of claim ~~20~~15, wherein said ~~second component of said drug composition is L DOPA and at least one compound selected from the group consisting of~~ dopaminergic agonist is bromocriptine or piribedil~~biperiden~~.

22. (Twice Amended) The method of claim ~~16~~15, wherein said drug composition is administered transdermally, subcutaneously, by using an extracorporeal pump~~extracoporeally~~ or orally.

24. (Twice Amended) The method of claim ~~20~~15, wherein said first component is administered at a gradually increasing rate.

26. (Amended) The method of claim 25 wherein ~~at about the time the maximum rate of administration of said first component is reached,~~ the effective dose of said L-DOPA is at least 30% lower than the effective dose when L-DOPA is administered in the absence of said first component.

28. (Twice amended) A method for treating a neurodegenerative disease, a multi-systemic atrophy, or both, in a human mammal comprising administering over a long term period an effective dose of at least two drug components comprising as a first component, nicotine or a nicotine derivative, and a second component comprising ~~at least one member selected from the group consisting of~~ L-DOPA and a dopaminergic ~~agonists~~agonist.

31. (Twice Amended) The method of claim ~~30~~28 wherein said ~~second component of said drug composition is L-DOPA and at least one compound selected from the group consisting of~~ dopaminergic agonist is bromocriptine or piribedil or piribedil ~~biperiden~~.

32. (Amended) The method of claim 31 wherein said treatment enables multiplication, stimulation and ~~/or~~ increase of nicotinergic receptors and pre-synaptic and post-synaptic D1 and D2 receptors in the nigrostriatum zone.

33. (Twice Amended) The method of claim 28 wherein said drug composition is administered transdermally, subcutaneously, by using an extracorporeal pump~~extracoporeally~~ or orally.

34. (Amended) The method of claim ~~31~~28 wherein at least one of said drug components is in galenical form.

35. (Twice Amended) The method of claim ~~30~~28 wherein said first component is administered at a gradually increasing rate.

37. (Amended) The method of claim 36 wherein ~~at about the time the maximum rate of administration of said first component is reached,~~ the effective dose of said L-DOPA is at least 30% lower than the effective dose when L-DOPA is administered in the absence of said first component.

39. (Amended) The drug composition of claim 10 or claim 53 wherein said nicotine or ~~a~~said nicotine derivative is present in an amount sufficient to be administered to said subject at a rate of from 93 mg to 160 mg per day.

40. (Amended) The drug composition of claim 10 or claim 53 wherein said nicotine or ~~a~~said nicotine derivative is present in amount sufficient to be administered to ~~said~~a subject at a rate of from ~~1.57mg~~0.2mg to 5 mg per day per kilogram of body weight of said subject.

41. (Amended) The drug composition of claim 10 or claim 53~~any of claims 39 and 40~~ wherein said L-DOPA is present in an amount sufficient to be administered to ~~said~~a subject at a rate of 0.2 mg to 3 mg per day per kilogram of body weight of said subject.

44. (Amended) The method of ~~any of claims~~ claim 15 ~~and 28~~ wherein said administering is ~~[selected from the group consisting of]~~ continuous~~,~~ or progressive~~, and continuous and progressive~~.

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